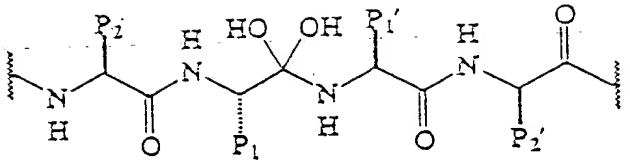
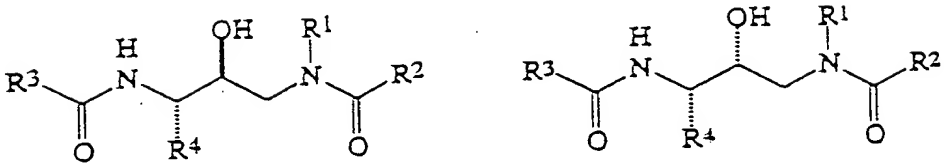


Intermediate of Peptide Hydrolysis



Hydroxyethylamine-Based Inhibitors

FIG. 1

08/820,904

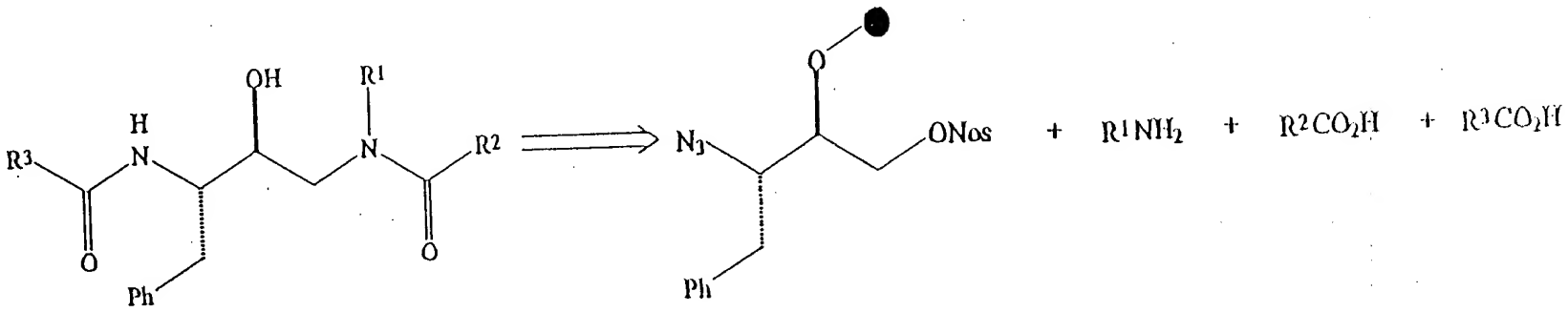


FIG. 2

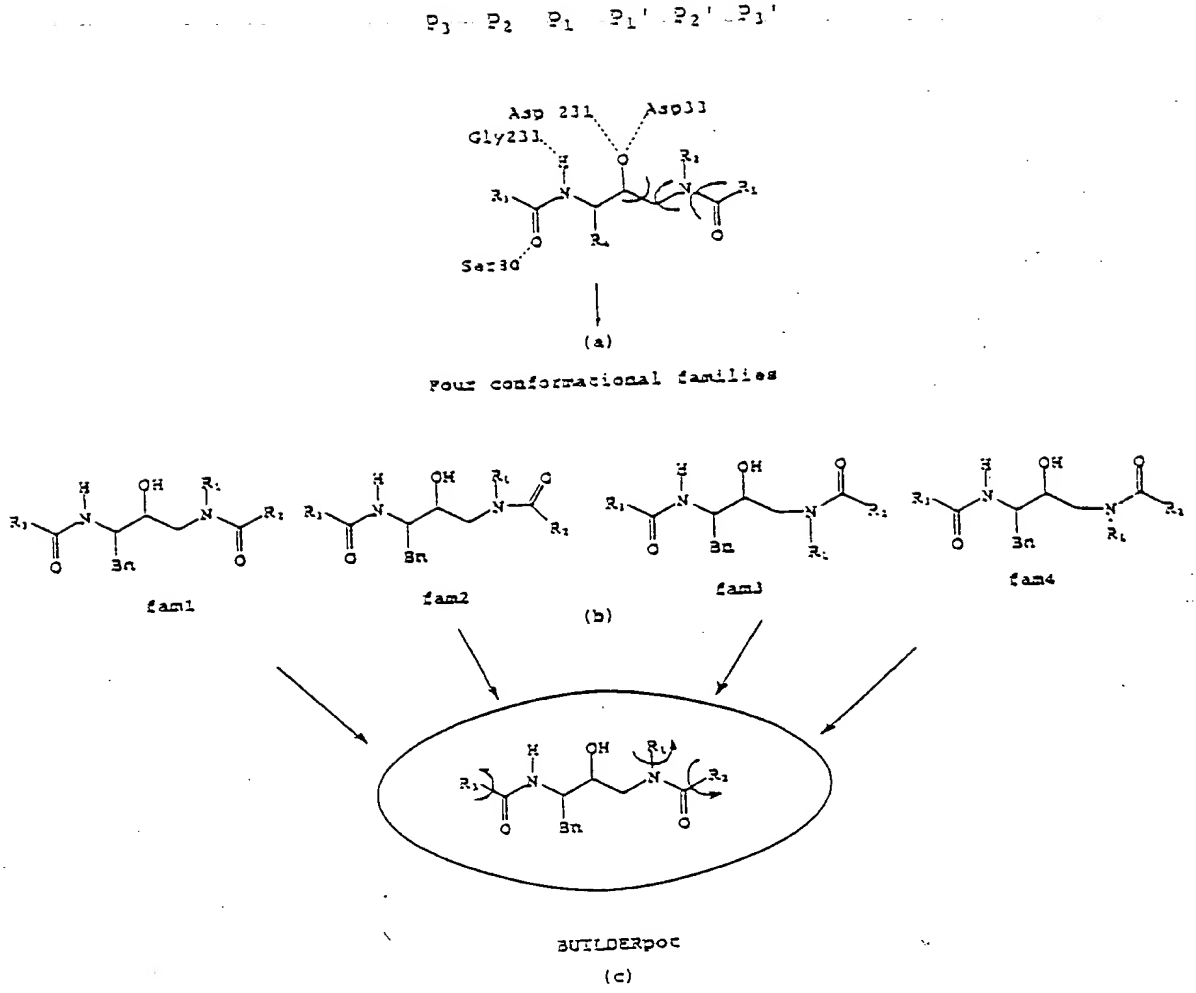

P3 P2 P1 P1' P2' P3'
Asp 231
Asp33
Gly231
Ser30
(a)
Four conformational families
fam1
fam2
fam3
fam4
(b)
BUILDERpoc
(c)

FIG. 3

08n220 "902n2560

R_1 substituent

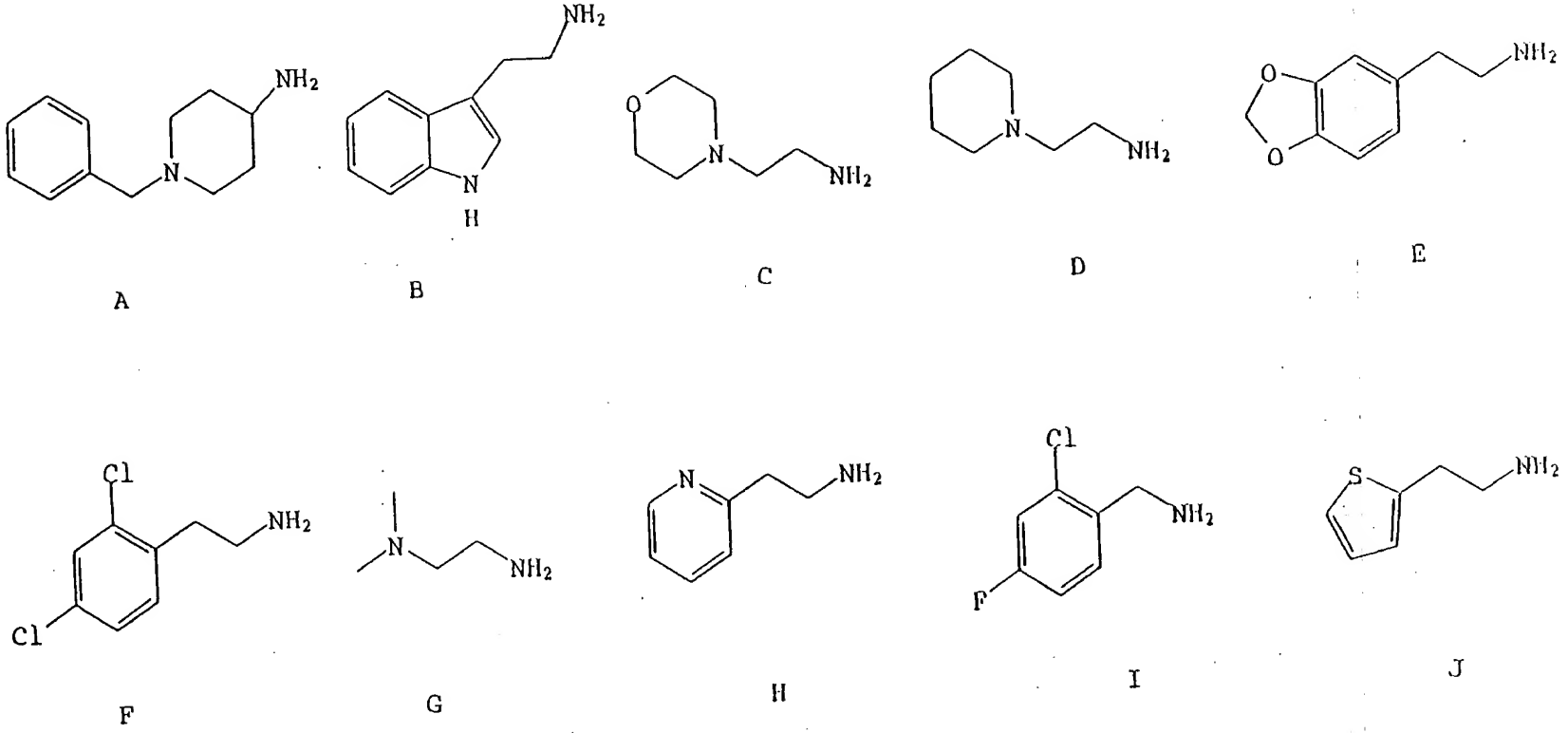
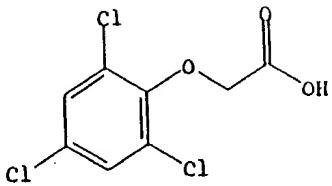
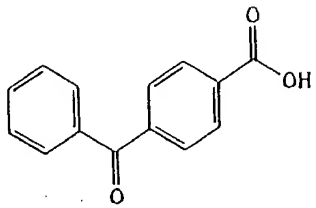


FIG. 4A

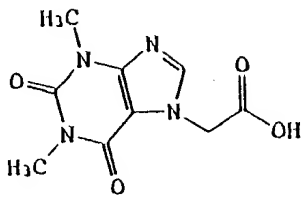
R_2 substituent



A



B



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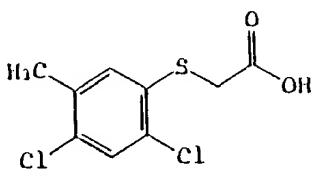

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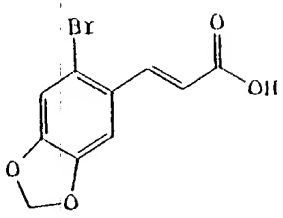
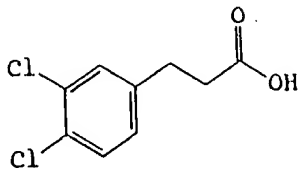
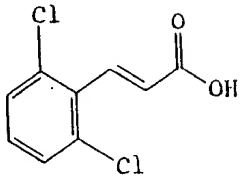


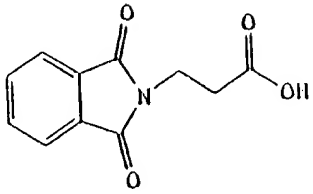
E



F



G



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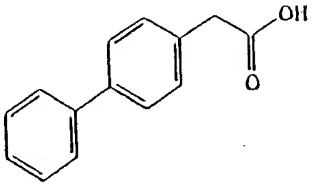

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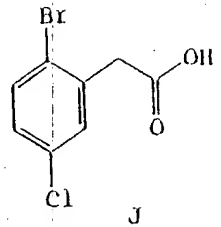
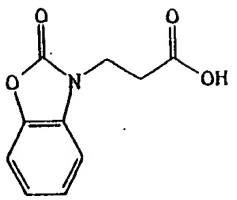


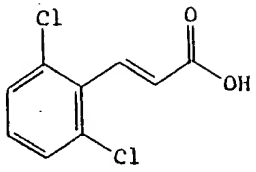
J

FIG. 4B

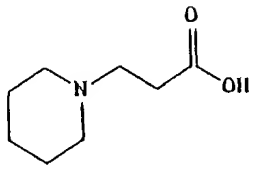
R_3 substituent



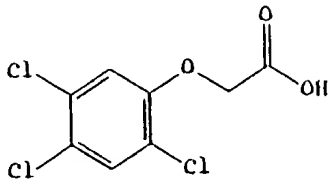
A



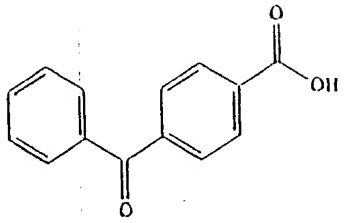
B



C



D



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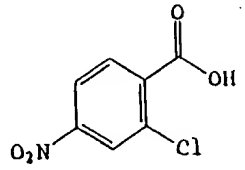

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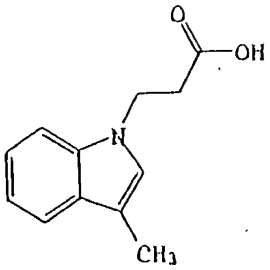

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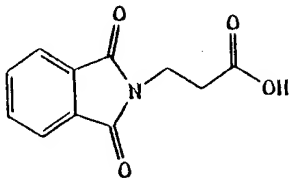

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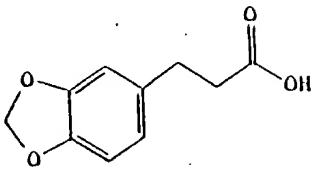
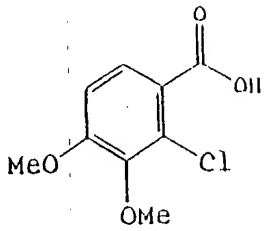


I



J

FIG. 4C

095347 06.032400

R_1 substituent

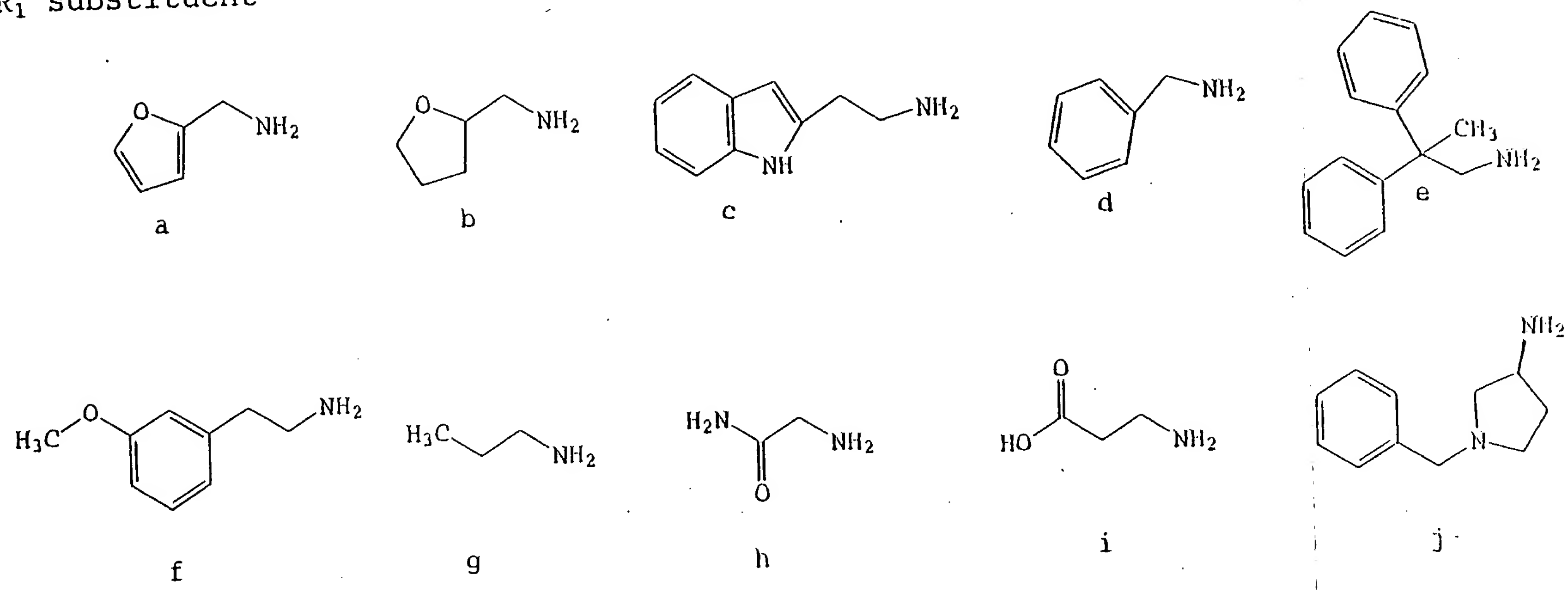


FIG. 5A

R_2 substituent

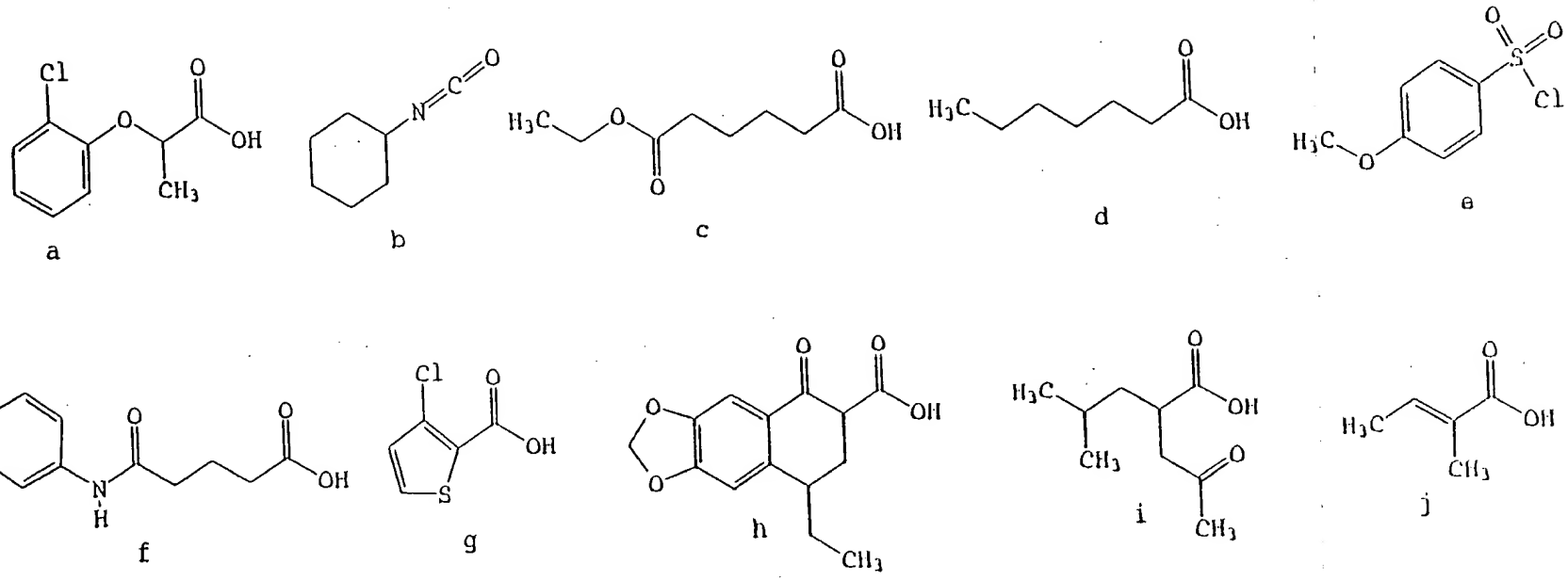
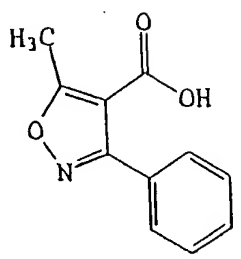


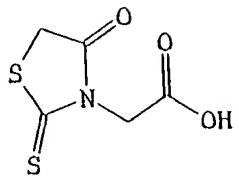
FIG. 5B

08320 9624560

R_3 substituent



a



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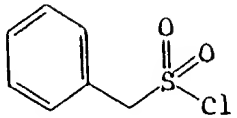

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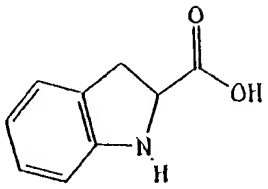

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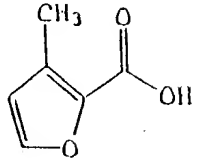

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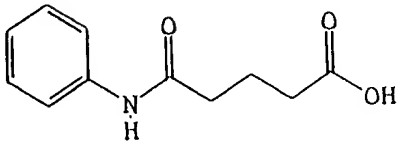

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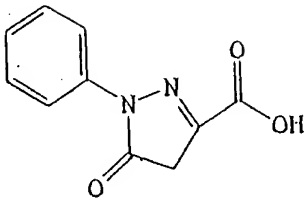

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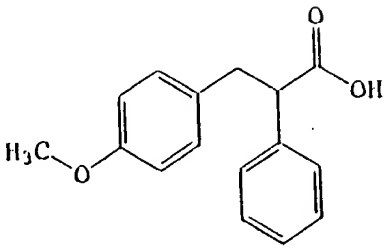

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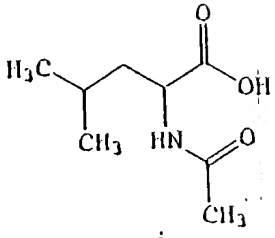

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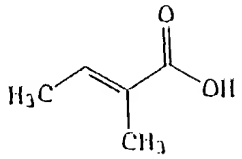
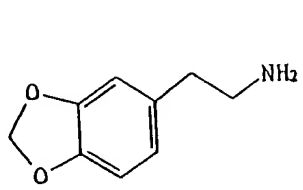


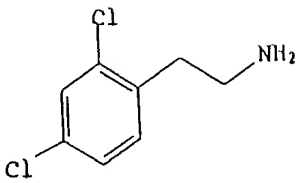
j

FIG. 5C

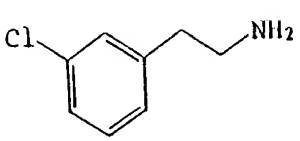
R_1 substituent



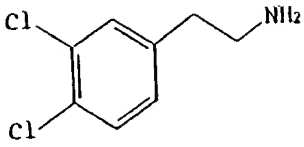
E



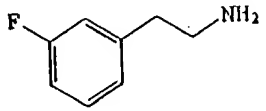
F



G



H



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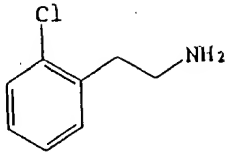

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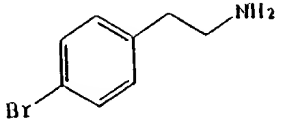

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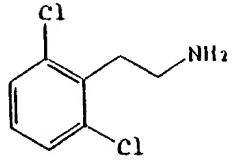

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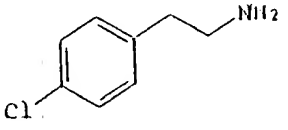

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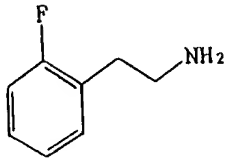

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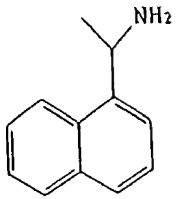
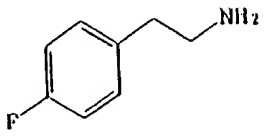
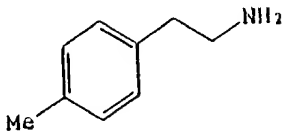


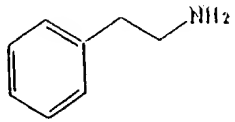
S



T



U

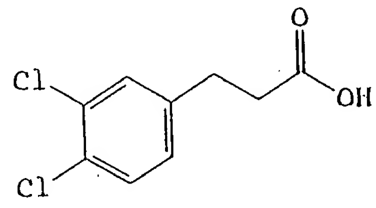


V

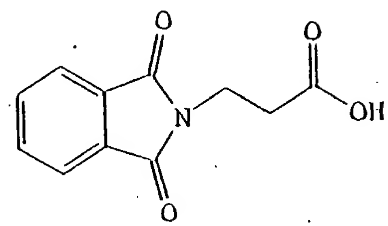
FIG. 6A

09534706.032400

R_2 substituent



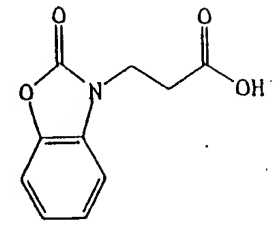
F



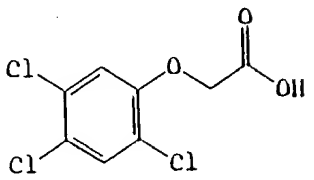
H

FIG. 6B

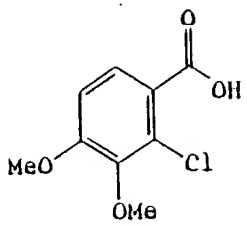
R_3 substituent



A



D



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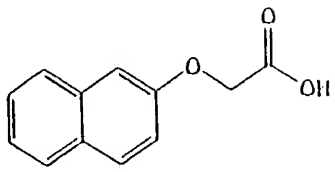
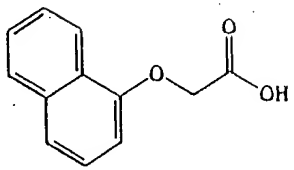
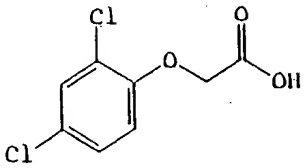


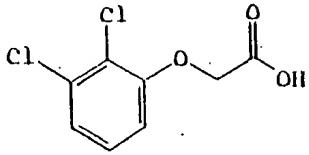
K



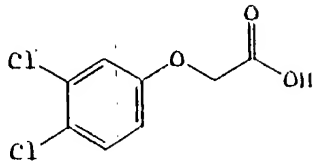
L



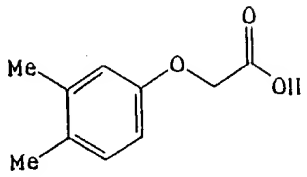
M



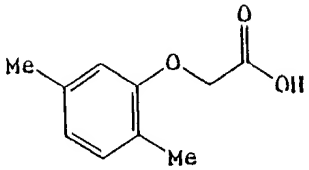
N



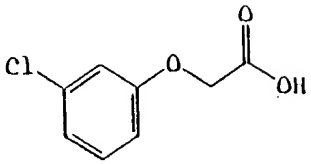
O



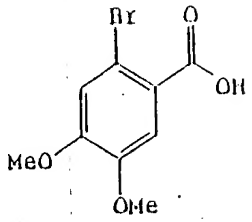
P



Q

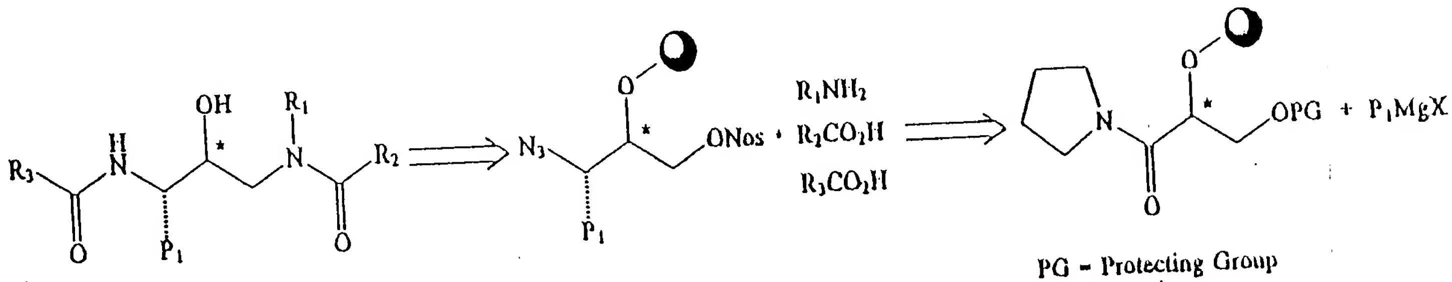


R



S

FIG. 6C



*1a = (*S*)-epimer
1b = (*R*)-epimer

*2a = (*S*)-epimer
2b = (*R*)-epimer

PG = Protecting Group
*3a = (*S*)-epimer
3b = (*R*)-epimer

FIG. 7

00h220" 90ZH£960

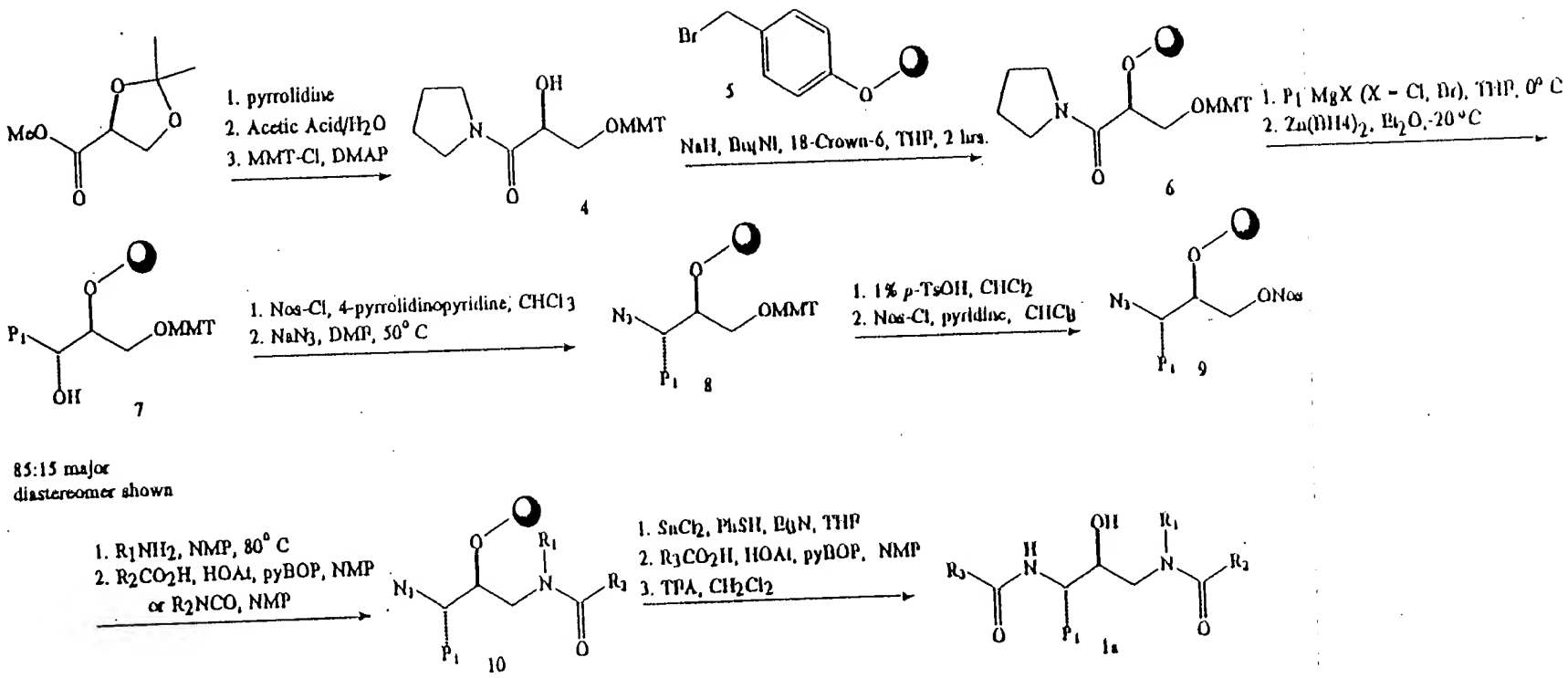


FIG. 8

09534706.022300

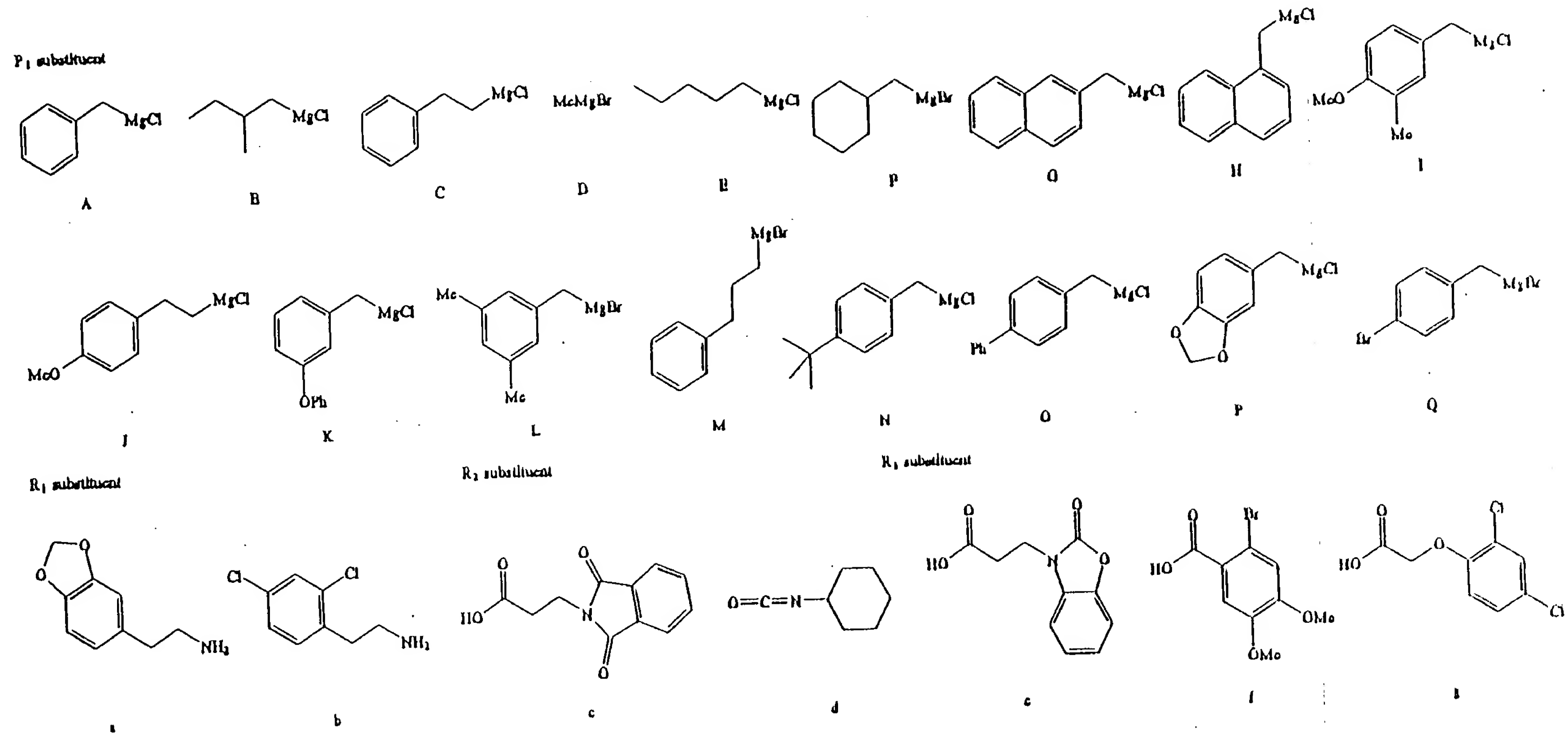


FIG. 9

00h20' 90ZhES60

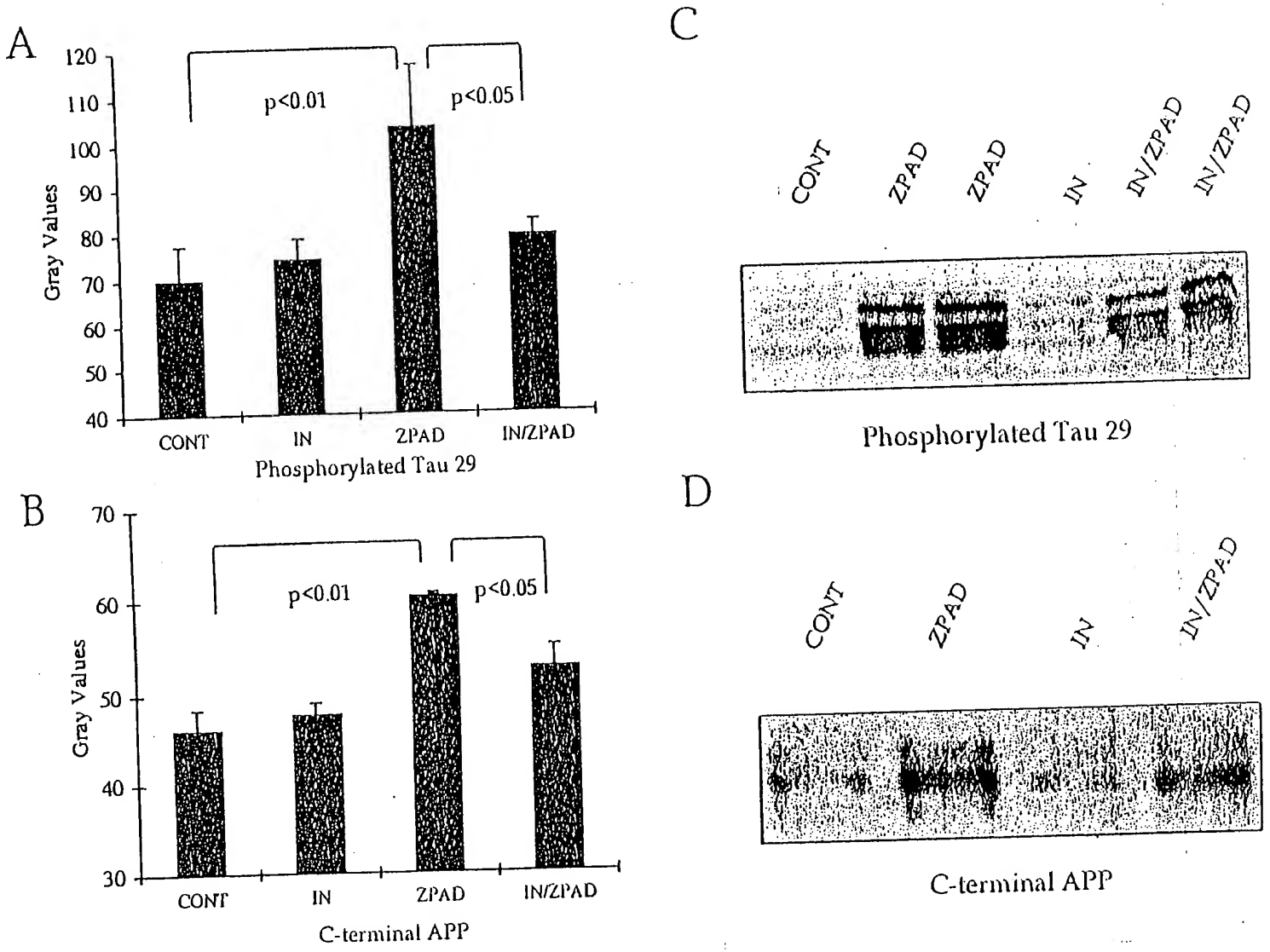


Figure 10

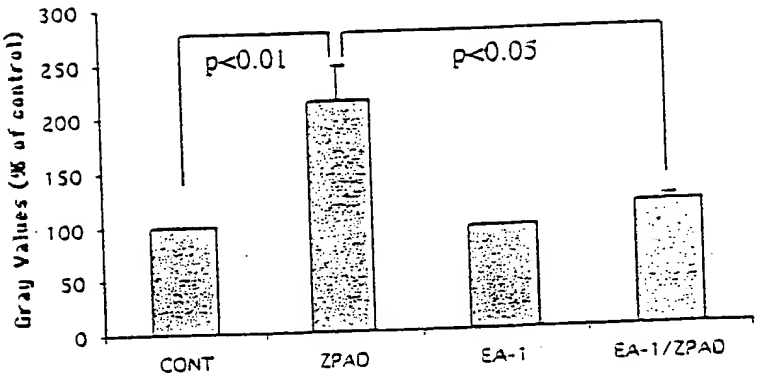

Gray Values (% of control)
300
250
200
150
100
50
0
p<0.01
p<0.05
CONT
ZPAD
EA-1
EA-1/ZPAD

Figure 11

Table 1 Cathepsin D inhibitors

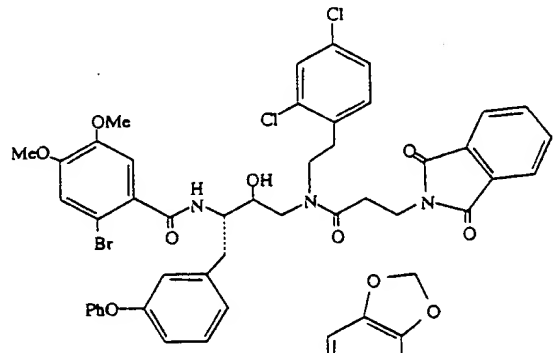
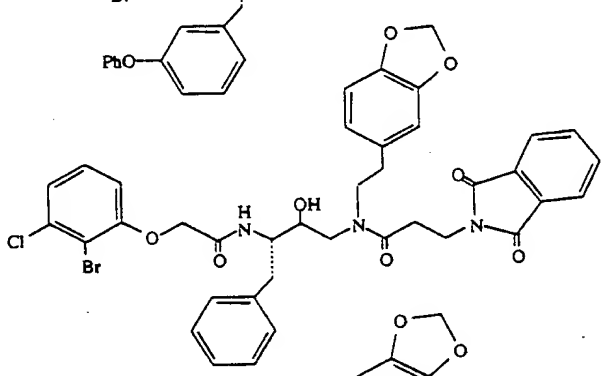
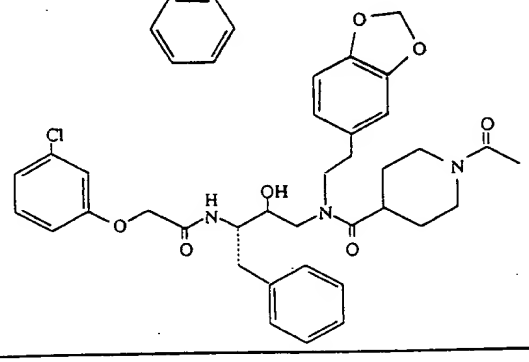
Name	Structures	Molecular Weight	Ki (nM)
CEL5-A		889.6	0.7
CEL5-G		697.2	15
EA-1		650	1.9

FIG. 12

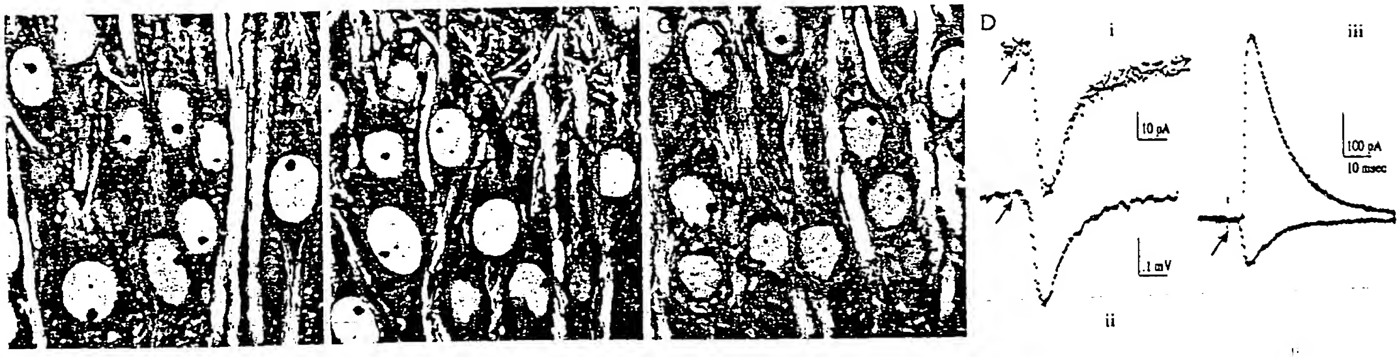


FIG. 13

09534705.032400

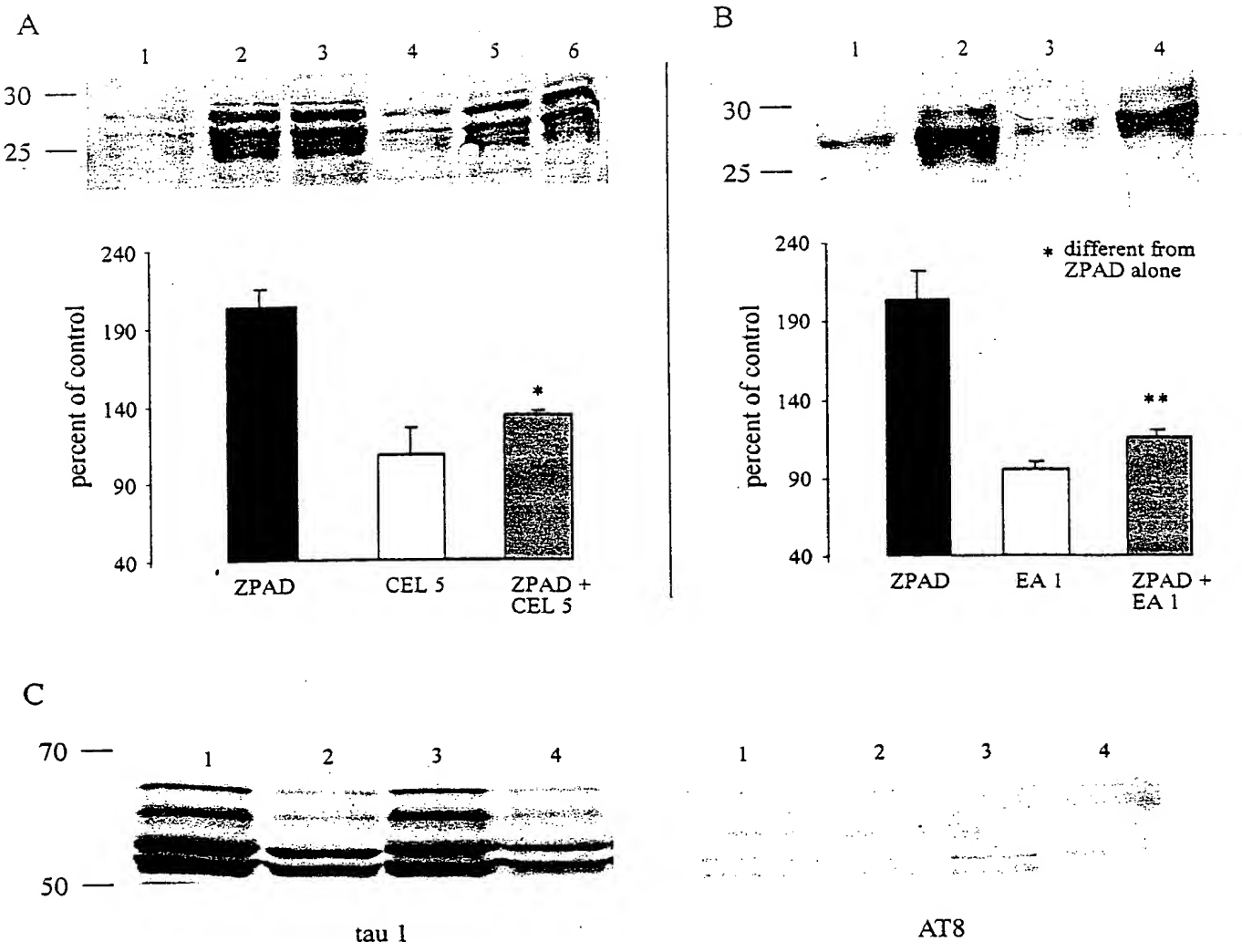

A
1
2
3
4
5
6
30
25
240
190
140
90
40
percent of control
*
ZPAD
CEL 5
ZPAD +
CEL 5
B
1
2
3
4
30
25
240
190
140
90
40
percent of control
* different from
ZPAD alone
**
ZPAD
EA 1
ZPAD +
EA 1
C
70
50
1
2
3
4
tau 1
1
2
3
4
AT8

FIG. 14

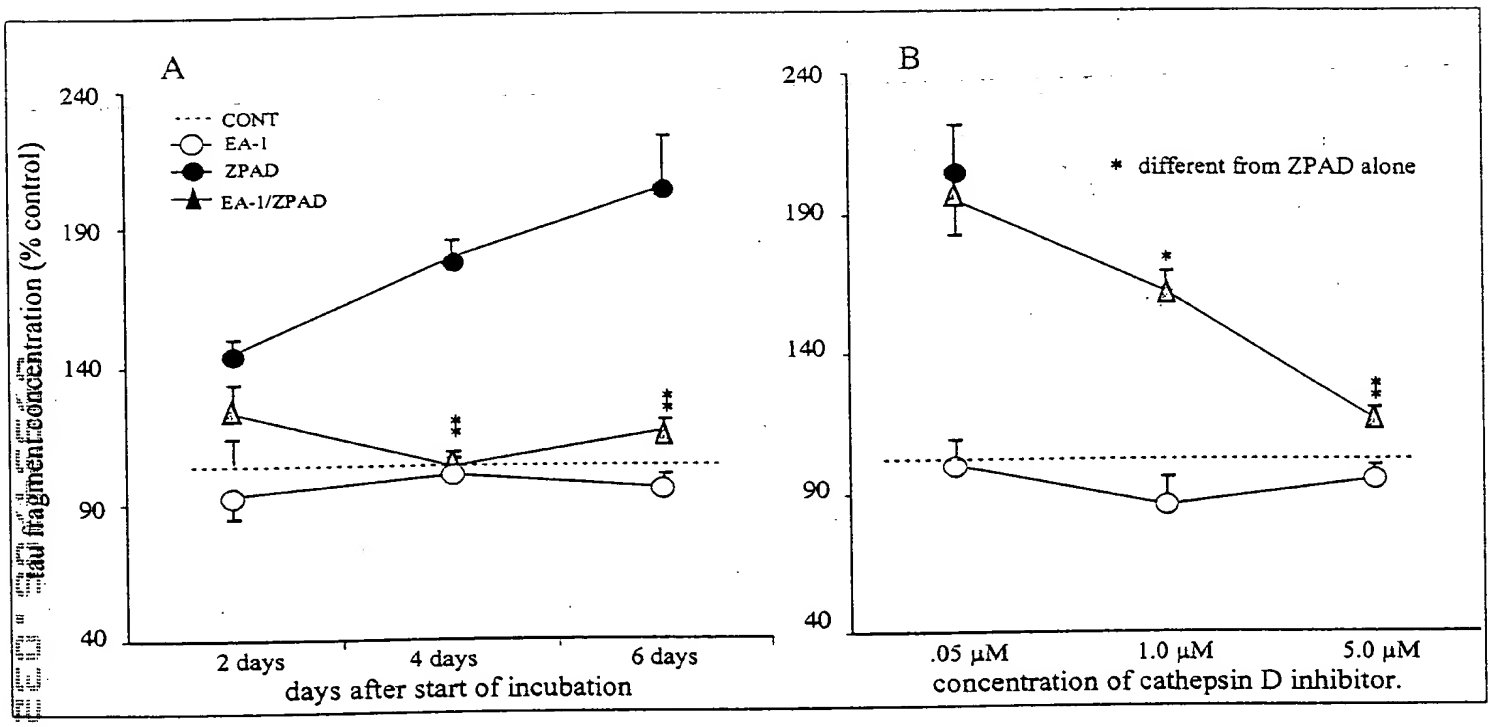

A
240
190
140
90
40
CONT
EA-1
ZPAD
EA-1/ZPAD
tau fragment concentration (% control)
2 days
4 days
6 days
days after start of incubation
B
240
190
140
90
40
* different from ZPAD alone
.05 μM
1.0 μM
5.0 μM
concentration of cathepsin D inhibitor.

FIG. 15

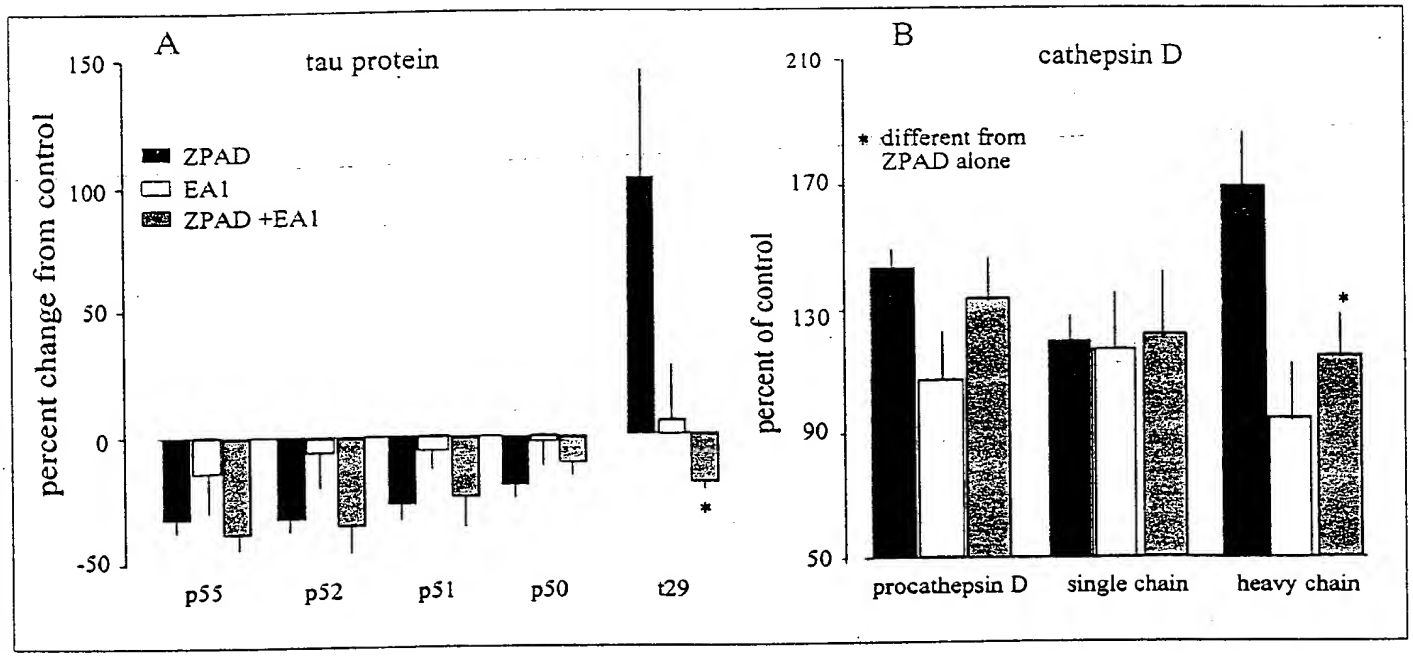

A
tau protein
percent change from control
150
100
50
0
-50
ZPAD
EA1
ZPAD +EA1
p55
p52
p51
p50
t29
*
B
cathepsin D
* different from ZPAD alone
percent of control
210
170
130
90
50
procathepsin D
single chain
heavy chain
*

FIG. 16